From the Lab Bench to the Clinic: Regulatory Issues in the Manufacture and Pre-clinical Testing of New Vaccines

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Regulatory Issues in the Manufacture and Pre-clinical Testing of Vaccines

- Current Good Manufacturing Practices
- Pre-clinical Product Testing
- Toxicology Testing

Focus of Phase I and Phase II studies

- Safety
- Immunogenicity
- Effectiveness

Current Good Manufacturing Practices

Current Good Manufacturing Practices Regulations

- CGMP Regulations (21 CFR 210 and 211)
- General Biologic Product Standards (21 CFR 610)
- IND Regulations (21 CFR 312)

Current Good Manufacturing Practices

- Facilities
- Raw Materials
- Components
- Equipment
- Validated Procedures
- Environmental Monitoring
- Personnel
- Documentation

CGMPs - Facilities

- Adequate space
- Systems for monitoring environmental conditions
- Systems for monitoring equipment
- Air supplied through HEPA filters
  - Class 100 - 3,520 particles, 1 microbe/ m^3
  - Class 100,000 – 3,520,000 particles, 100 microbes/ m^3

CGMPs – Raw Materials and Components

- Document Source of Raw Materials and Components
- Testing of Raw Materials and Components
- SOPs for Receipt, Quarantine, Storage, and Release
- Primary Packaging System Defined
- BSE Contamination

CGMPs – Monitoring of the Environment and Water

- Evaluate the quality of air and surfaces
  - Surface, active air, and passive air monitoring
- Monitor water supplies
  - Microbial Contamination
  - Chemical Content
  - Water for Injection used for Product Components
- SOPs
  - Frequency and Time of Sampling
  - Duration of Sampling

CGMPs - Personnel

- Most Common Cause of Manufacturing Deviations
- Adequate Training
- Experienced Supervisors
- Health Status Monitored

CGMPs – Batch Production Record

- Complete Record of Entire Manufacturing Process
- Documents Every Step in the Manufacturing Process
  - Raw Materials
  - Buffer and Media Production
  - Product Purification
  - Testing Results
  - Environmental Monitoring, etc.

CGMPs – Manufacturing Process Validation

- Entire Process standardized and validated (fermentation, harvesting, sterilization, cleaning, etc.)
- SOPs written for the entire Manufacturing Process
- Process standardization leads to Consistent Manufacturing

CGMP Summary

- Use Clean Air and Water
- Standardize and Validate the Manufacturing Process
- SOPs are Essential
- Document the Process

Pre-Clinical Product Testing

Characterization of the Product

- **Safety** (21 CFR 600.3)
  - ✓ Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...
- **Purity** (21 CFR 600.3)
  - ✓ Relative freedom from extraneous matter in the finished product...
- **Potency** (21 CFR 600.3)
  - ✓ Specific capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Product Testing

- General Safety
- Sterility
- Potency
- Purity
- Identity
- Toxicology
- Other relevant safety assays
- Stability

General Safety

- Detection of extraneous toxic contaminants
- Required for biological products
- Method in 21 CFR 610.11
  - Injection into mice and guinea pigs
  - 7 day test period
  - Survival
  - Weight gain

Sterility

- Freedom from contaminating organisms
- 21 CFR 610.12 sterility test procedure
  - Fluid thioglycolate media
  - Soybean casein digest media
  - Strains to test for growth promotion of media
- Equivalent methods – USP methods
- Bioburden assessments required for live attenuated vaccine strains

Potency

- Specific capacity to effect a given result
- Often shows that a biologic induces an appropriate immune response
- May not directly correlate with product efficacy
- In vivo or in vitro
- Measure of manufacturing consistency and stability

Types of Vaccine Potency Assays

- Mouse Protection Assay – Typhoid, Plague
- Guinea Pig Protection – Anthrax
- Toxin Neutralization – Tetanus, Diptheria
- Viability – BCG
- DTH response – BCG
- ELISA to specific antigens – Acellular pertussis
- Saccharide/protein ratio – Pneumococcal, Haemophilus polysaccharide conjugates

Purity

- Free of Extraneous Materials
- Moisture
- Pyrogenicity
- Adventitious Agents
- Chemical Composition
- SDS PAGE, HPLC, Mass Spec, NMR, etc.

Vaccine Specific Safety Issues

- DNA Vaccines
  - Germline integration
  - Tissue distribution
- Live, Attenuated Vaccines
  - Reversion frequency
  - Definition of genetic mutations
- Subunit Vaccines
  - Toxicity of adjuvants
  - Endotoxin contamination

Stability

- Defines product shelf-life (1 – 2 yrs)
- Stable product needed for clinical trials
- Establish program to evaluate stability at specific time intervals
  - Potency
  - Moisture
  - Sterility

Vaccine Toxicology Studies

Vaccine Toxicology

- To support entry into clinical trials
- Maximize benefit-to-risk ratio
- Determine a safe dose
- Identify potential and unknown toxicities to target organs

Toxicity Studies: General Principles

- Ideally, use same lot as used in proposed clinical study
- Route of administration and vaccine dose should correspond to clinical study
- Total number of doses equal or exceed number of clinically administered doses (n+1)

Toxicity Assessment: Animal Models

- Test relevant animal species
- An animal species which responds to the activity of the product (immune response generated)
- Ideally, animal species sensitive to specific challenge with pathogen or toxin
- One animal species is generally sufficient
- Group size dependent on animal model

Toxicity Assessment: Parameters Monitored

- Local – Systemic Events
- General Clinical Observations (good health, wt. gain)
- Immunogenicity
- Serum chemistry
- Hematologic Analysis
- Injection Site Histopathology
- Terminal Procedures (necropsy, organ evaluation, tissue histopathology)

Vaccine Manufacturing Submissions: Common Concerns

- Insufficient information and documentation
- Clinical lots not clearly identified
- Inadequate product testing results
- Inappropriate testing for adventitious agents or toxic components

Vaccine Manufacturing Submissions: Common Concerns (cont.)

- Inadequate stability testing
- Inappropriate toxicology testing
- Pre-clinical testing formulation differs from clinical vaccine formulation

CBER Guidance

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